EMORY
WINSHIP
CANCER
INSTITUTE
National Cancer Institute-Designated
Comprehensive Cancer Center

Role of Immunotherapy in the Perioperative Management of NSCLC

Ticiana Leal, MD
Associate Professor of Medicine
Diretor, Thoracic Oncology Program
Winship Cancer Institute
Emory University

Disclosures

Ticiana A. Leal, MD (past 12 months)

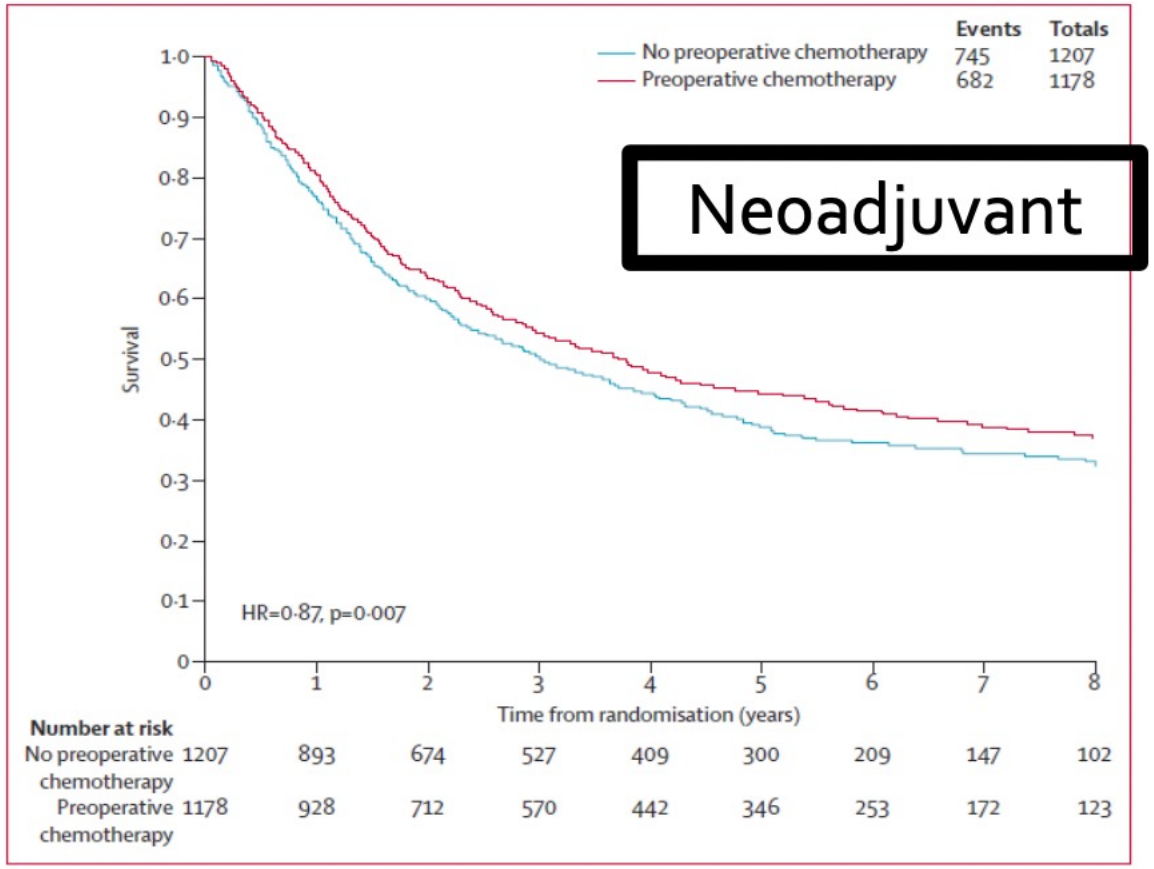
- **Advisory Board:**
  - Blueprint, Merck, AstraZeneca, Jazz, Boehringer-Ingelheim, Bayer, Mirati
- **Consulting:**
  - Jazz, Boehringer-Ingelheim, Genentech, Lilly, Janssen

Introduction

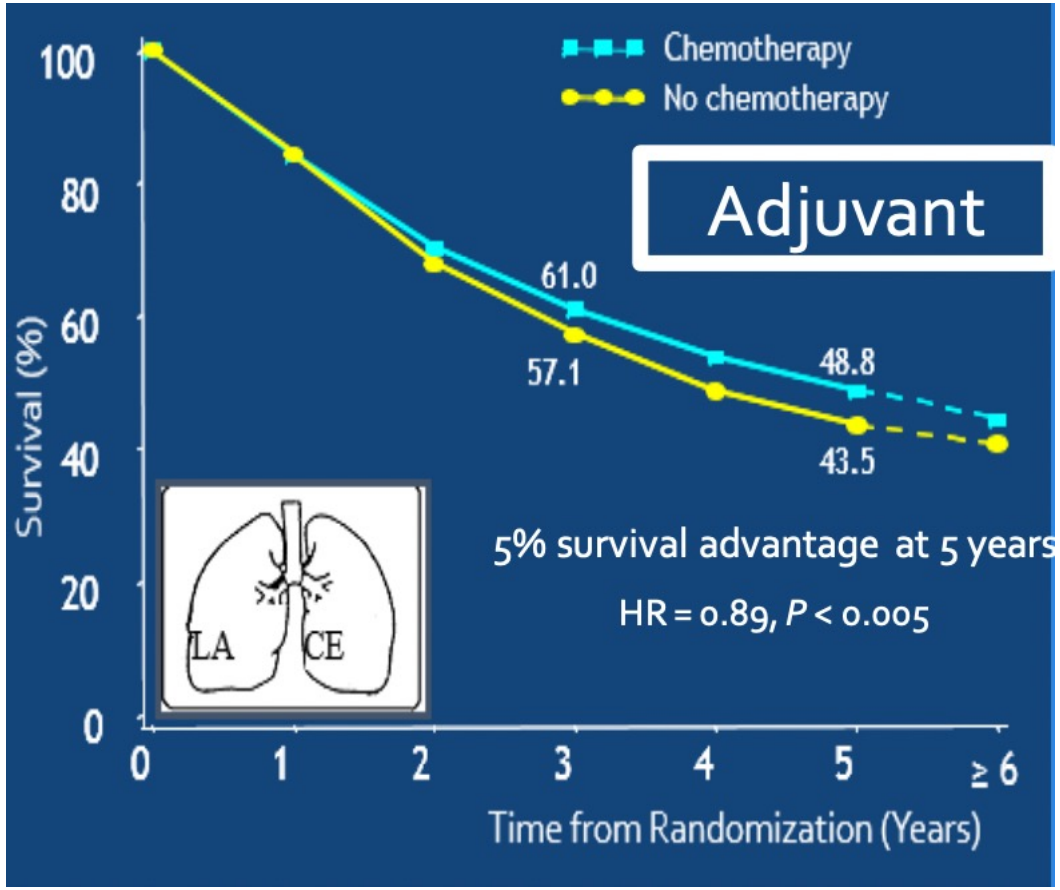
- Approximately 30% of patients with NSCLC present with resectable early-stage disease at the time of diagnosis; even with complete surgical resection, there is a significant risk of disease recurrence.
- The gains associated with use of perioperative chemotherapy have led to modest improvements in overall survival, though pathological complete responses are uncommon (<5%).

Forde et al. NEJM 2022
Arriagada et al. Lancet 2010
Leal, Ramalingam. Cell Reports Medicine 2022

Neoadjuvant versus adjuvant therapy



Vs.



NSCLC Meta-Analysis Group. Lancet Oncology 2014
Pignon et al. JCO 2006

Perioperative immunotherapy trials

	Study (Primary Endpoint)	Patient population
Neoadjuvant	CheckMate 816 (pCR, EFS)* FDA approval	Excludes EGFR/ALK
Neoadjuvant/adj	Checkmate 77T (EFS)	Excludes EGFR/ALK
Neoadjuvant/adj	Aegean (pCR, EFS)	Excludes EGFR/ALK
Neoadjuvant/adj	KEYNOTE 671 (EFS, OS)	May include EGFR/ALK
Neoadjuvant/adj	IMpower030 (EFS)	Excludes EGFR/ALK
Adjuvant	IMpower010 (DFS)* FDA approval	May include EGFR/ALK
Adjuvant	PEARLS/KN 091 (DFS)	May include EGFR/ALK
Adjuvant	BR.31 (DFS in PD-L1 TC ≥ 25%	May include EGFR/ALK
Adjuvant	ANVIL (DFS, OS)	Excludes EGFR/ALK

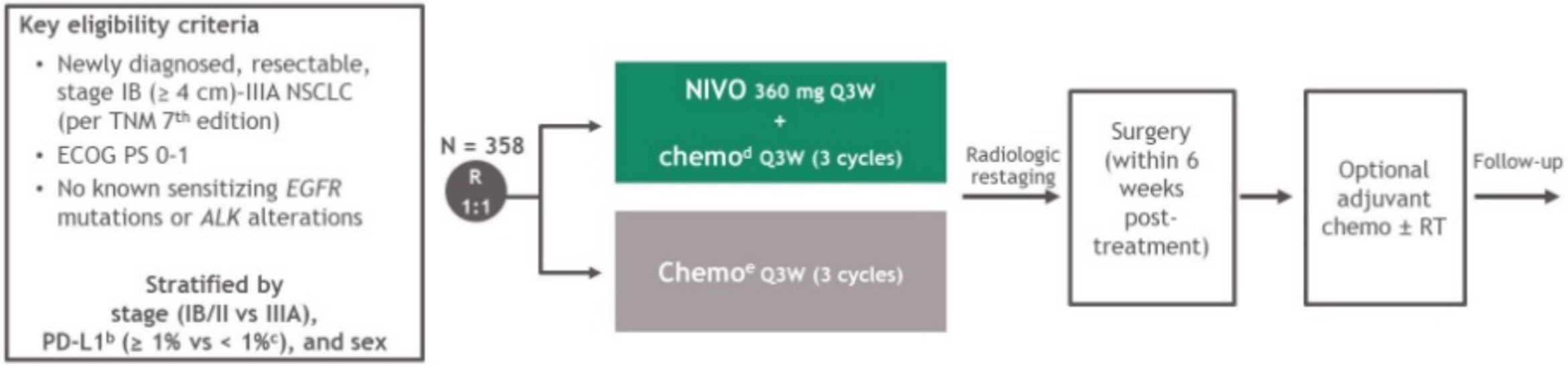
Forde et al. NEJM 2022; Cascone et al. ASCO 2021;
Felip et al. Lancet 2021;
Paz-Ares et al. ESMO Virtual Plenary 2022

Phase II trials neoadjuvant IO+/- chemo

	Author(s)	Agent(s)	MPR% (95% CI)	pCR% (95% CI)
Johns Hopkins University/Memorial Sloan Kettering N=21	Forde and Chaft	Nivolumab	43% (21 to 66)	14% (4 to 34)
LCMC3 Lung Cancer Mutation Consortium - USA N=181	Carbone	Atezolizumab	21% (14 to 28)	7% (2 to 12)
NEOSTAR MD Anderson N=44	Cascone	Nivolumab plus Ipilimumab Nivolumab	50% 24%	38% 10%
NADIM Spanish Lung Cancer Group N=46	Provencio	Nivolumab + Paclitaxel Carboplatin	80% (64 to 91)	75% (4 to 76)
Columbia University NewYork/MGH N=30	Shu	Atezolizumab + Paclitaxel Carboplatin	57% (36 to 76)	33% (18 to 52)
Duke/Dartmouth/Mayo N=25	Ready	Pembrolizumab	28% (12 to 49)	8% (1 to 26)

Kris ASCO Ed 2020.

CheckMate 816



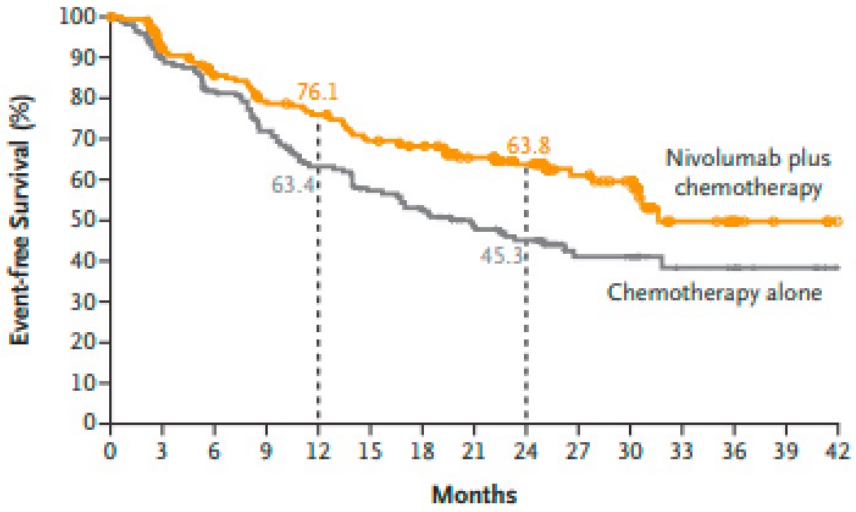
Primary endpoints
- pCR by BIPR
- EFS by BICR

Key secondary endpoints
- MPR by BIPR
- OS
- Time to death or distant metastases

Key exploratory endpoints included
- ORR by BICR
- Feasibility of surgery; peri- and post-operative surgery-related AEs

Forde et al. NEJM 2022

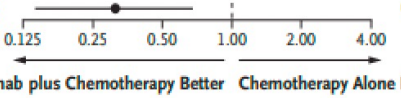
CheckMate 816: EFS benefit



	No. of Patients	Median Event-free Survival (95% CI) mo
Nivolumab plus Chemotherapy	179	31.6 (30.2–NR)
Chemotherapy Alone	179	20.8 (14.0–26.7)

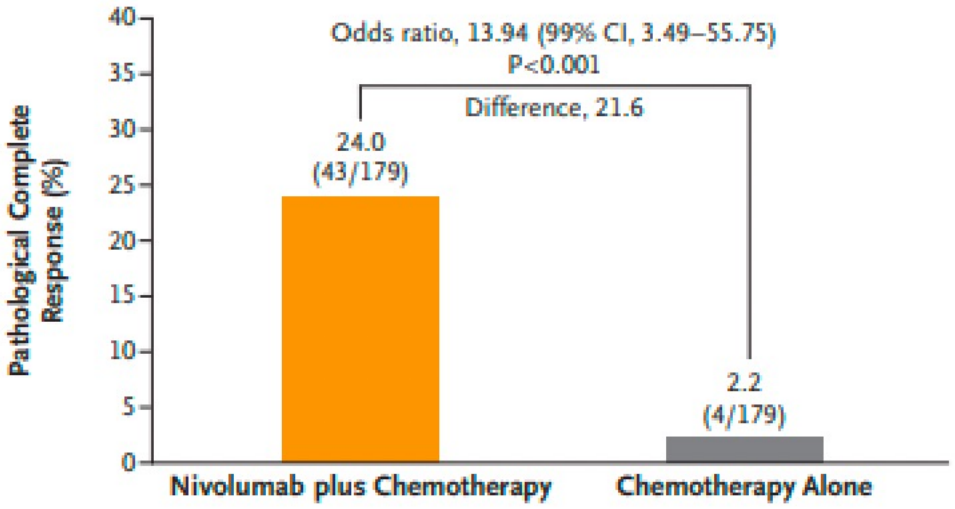
Hazard ratio for disease progression, disease recurrence, or death, 0.63 (97.38% CI, 0.43–0.91)
P=0.005

Subgroup	No. of Patients	Median Event-free Survival (95% CI) mo: Nivolumab plus chemotherapy (N=179)	Median Event-free Survival (95% CI) mo: Chemotherapy alone (N=179)	Unstratified Hazard Ratio for Disease Progression, Disease Recurrence, or Death (95% CI)
Overall	358	31.6 (30.2–NR)	20.8 (14.0–26.7)	0.63 (0.45–0.87)
Age				
<65 yr	176	NR (31.6–NR)	20.8 (14.0–NR)	0.57 (0.35–0.93)
≥65 yr	182	30.2 (23.4–NR)	18.4 (10.6–31.8)	0.70 (0.45–1.08)
Sex				
Male	255	30.6 (20.0–NR)	16.9 (13.8–24.9)	0.68 (0.47–0.98)
Female	103	NR (30.5–NR)	31.8 (13.9–NR)	0.46 (0.22–0.96)
Geographic region				
North America	91	NR (25.1–NR)	NR (12.8–NR)	0.78 (0.38–1.62)
Europe	66	31.6 (13.4–NR)	21.1 (10.2–NR)	0.80 (0.36–1.77)
Asia	177	NR (30.2–NR)	16.5 (10.8–22.7)	0.45 (0.29–0.71)
ECOG performance-status score				
0	241	NR (30.2–NR)	22.7 (16.6–NR)	0.61 (0.41–0.91)
1	117	30.5 (14.6–NR)	14.0 (9.8–26.2)	0.71 (0.41–1.21)
Disease stage at baseline				
IB or II	127	NR (27.8–NR)	NR (16.8–NR)	0.87 (0.48–1.56)
IIIA	228	31.6 (26.6–NR)	15.7 (10.8–22.7)	0.54 (0.37–0.80)
Histologic type of tumor				
Squamous	182	30.6 (20.0–NR)	22.7 (11.5–NR)	0.77 (0.49–1.22)
Nonsquamous	176	NR (27.8–NR)	19.6 (13.8–26.2)	0.50 (0.32–0.79)
Smoking status				
Current or former smoker	318	31.6 (30.2–NR)	22.4 (15.7–NR)	0.68 (0.48–0.96)
Never smoked	39	NR (5.6–NR)	10.4 (7.7–20.8)	0.33 (0.13–0.87)
PD-L1 expression level				
<1%	155	25.1 (14.6–NR)	18.4 (13.9–26.2)	0.85 (0.54–1.32)
≥1%	178	NR (NR–NR)	21.1 (11.5–NR)	0.41 (0.24–0.70)
1–49%	98	NR (27.8–NR)	26.7 (11.5–NR)	0.58 (0.30–1.12)
≥50%	80	NR (NR–NR)	19.6 (8.2–NR)	0.24 (0.10–0.61)
TMB				
<12.3 mutations/megabase	102	30.5 (19.4–NR)	26.7 (16.6–NR)	0.86 (0.47–1.57)
≥12.3 mutations/megabase	76	NR (14.8–NR)	22.4 (13.4–NR)	0.69 (0.33–1.46)
Type of platinum therapy				
Cisplatin	258	NR (25.1–NR)	20.9 (15.7–NR)	0.71 (0.49–1.03)
Carboplatin	72	NR (30.5–NR)	10.6 (7.6–26.7)	0.31 (0.14–0.67)



Forde et al. NEJM 2022

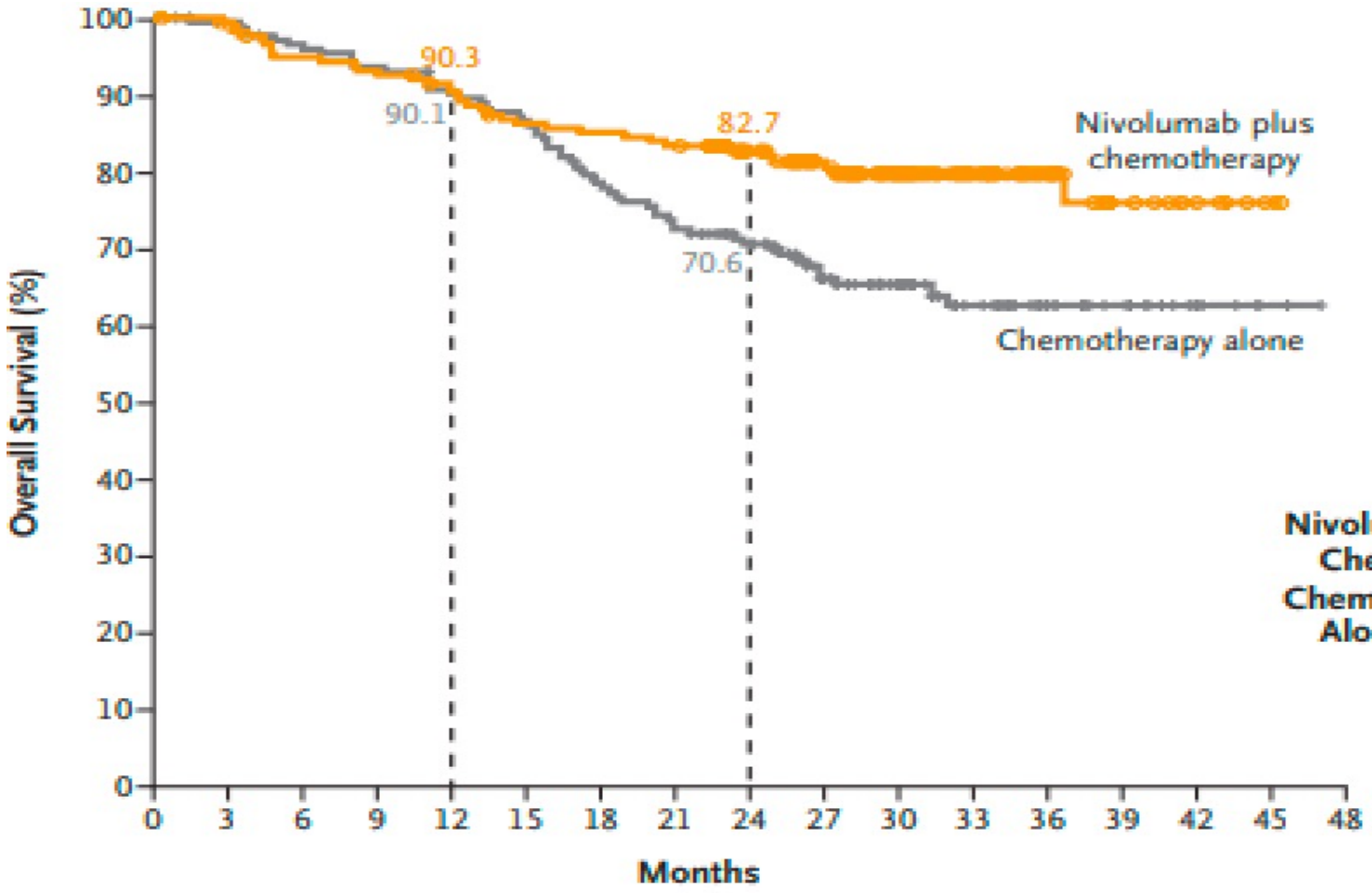
CheckMate 816: Path CR



Subgroup	No. of Patients	Pathological Complete Response (95% CI)		Unweighted Difference, Nivolumab plus Chemotherapy minus Chemotherapy Alone (95% CI)
		Chemotherapy alone (N=179)	Nivolumab plus chemotherapy (N=179)	
		%		*percentage points*
Overall	358	2.2 (0.6–5.6)	24.0 (18.0–31.0)	21.8 (15.2 to 28.7)
Age				
<65 yr	176	0 (0–4.3)	26.9 (18.2–37.1)	26.9 (17.8 to 36.7)
≥65 yr	182	4.2 (1.1–10.3)	20.9 (12.9–31.0)	17.8 (7.3 to 26.8)
Sex				
Male	255	2.4 (0.5–6.7)	22.7 (15.7–30.9)	20.3 (12.6 to 28.4)
Female	103	1.9 (<0.1–10.3)	27.5 (15.9–41.7)	25.5 (12.3 to 39.1)
Geographic region				
North America	91	2.0 (<0.1–10.6)	22.0 (10.6–37.6)	20.0 (6.9 to 34.8)
Europe	66	0 (0–13.7)	24.4 (12.4–40.3)	24.4 (7.4 to 39.3)
Asia	177	3.3 (0.7–9.2)	28.2 (19.0–39.0)	25.0 (14.7 to 35.5)
ECOG performance-status score				
0	241	1.7 (0.2–6.0)	26.9 (19.1–35.3)	24.9 (16.7 to 33.4)
1	117	3.2 (0.4–11.2)	18.2 (9.1–30.9)	15.0 (3.8 to 27.3)
Disease stage at baseline				
IB or II	128	4.8 (1.0–13.3)	26.2 (16.0–38.5)	21.4 (9.0 to 33.6)
IIIA	228	0.9 (<0.1–4.7)	23.0 (15.6–31.9)	22.1 (14.3 to 30.7)
Histologic type of tumor				
Squamous	182	4.2 (1.2–10.4)	25.3 (16.6–35.7)	21.1 (11.0 to 31.4)
Nonsquamous	176	0 (0–4.3)	22.8 (14.7–32.8)	22.8 (14.2 to 32.4)
Smoking status				
Current or former smoker	318	2.5 (0.7–6.4)	25.6 (19.1–33.1)	23.1 (15.9 to 30.5)
Never smoked	39	0 (0–16.8)	10.5 (1.3–33.1)	10.5 (–7.3 to 31.4)
PD-L1 expression level				
<1%	155	2.6 (0.3–9.1)	16.7 (9.2–26.8)	14.1 (4.8 to 24.0)
≥1%	178	2.2 (0.3–7.9)	32.6 (23.0–43.3)	30.3 (19.9 to 40.7)
1–49%	98	0 (0–7.5)	23.5 (12.8–37.5)	23.5 (11.4 to 36.8)
≥50%	80	4.8 (0.6–16.2)	44.7 (28.6–61.7)	40.0 (21.7 to 55.9)
TMB				
<12.3 mutations/megabase	102	1.9 (<0.1–10.1)	22.4 (11.8–36.6)	20.6 (8.2 to 34.1)
≥12.3 mutations/megabase	76	2.7 (<0.1–14.2)	30.8 (17.0–47.6)	28.1 (11.6 to 43.9)
Type of platinum therapy				
Cisplatin	258	2.2 (0.5–6.4)	21.8 (14.9–30.1)	19.5 (12.0 to 27.7)
Carboplatin	72	0 (0–10.6)	30.8 (17.0–47.6)	30.8 (14.7 to 46.4)

Forde et al. NEJM 2022

CheckMate 816: OS

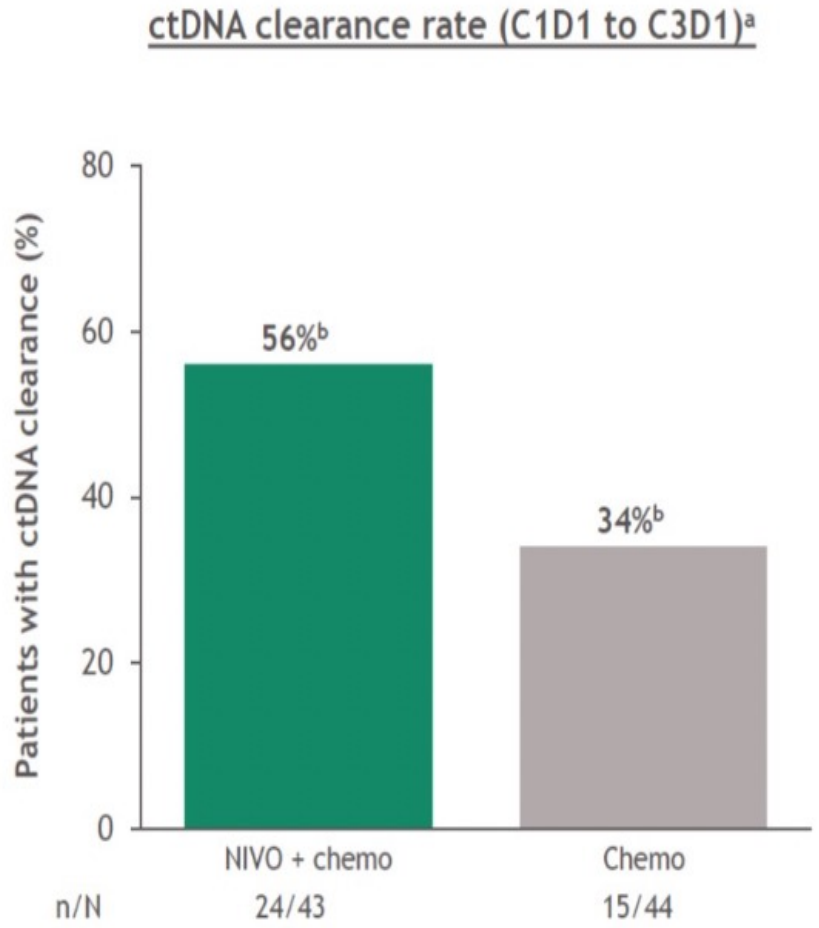


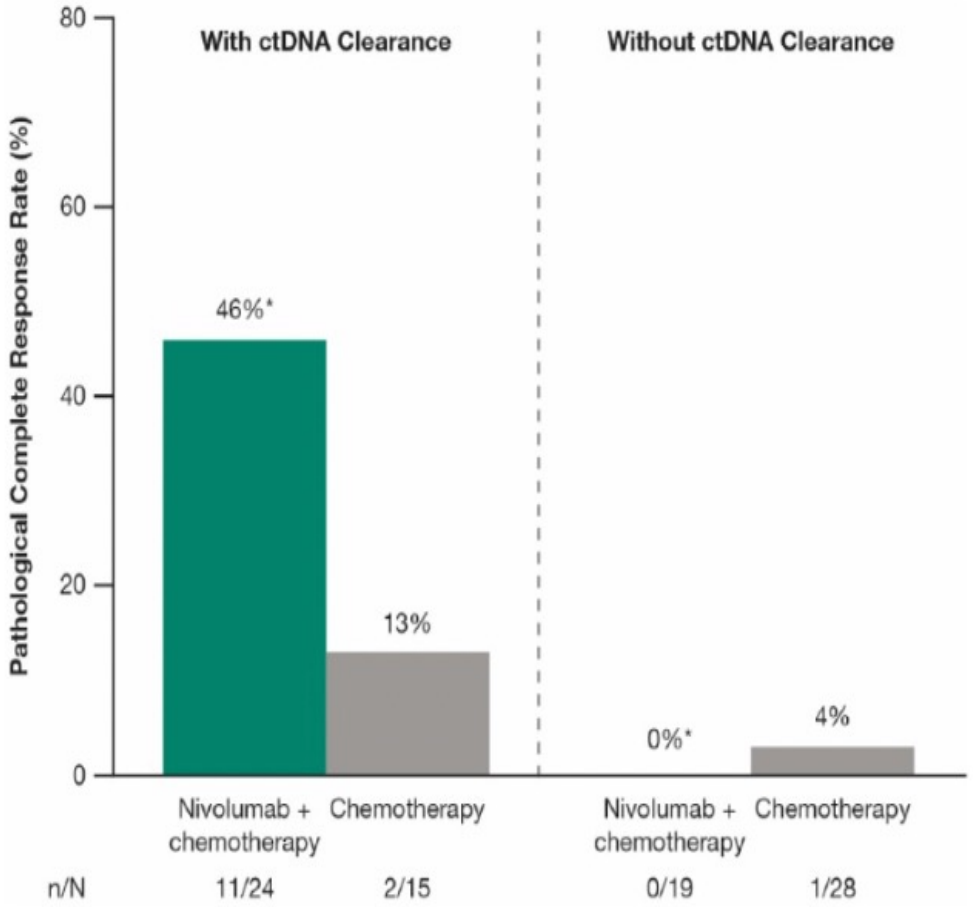
	No. of Patients	Median Overall Survival (95% CI) *mo*
Nivolumab plus Chemotherapy	179	NR (NR–NR)
Chemotherapy Alone	179	NR (NR–NR)

Hazard ratio for death, 0.57
(99.67% CI, 0.30–1.07)
P=0.008

Forde et al. NEJM 2022

ctDNA clearance and association with pCR in CheckMate-816





Forde PM et al. *NEJM* 2022

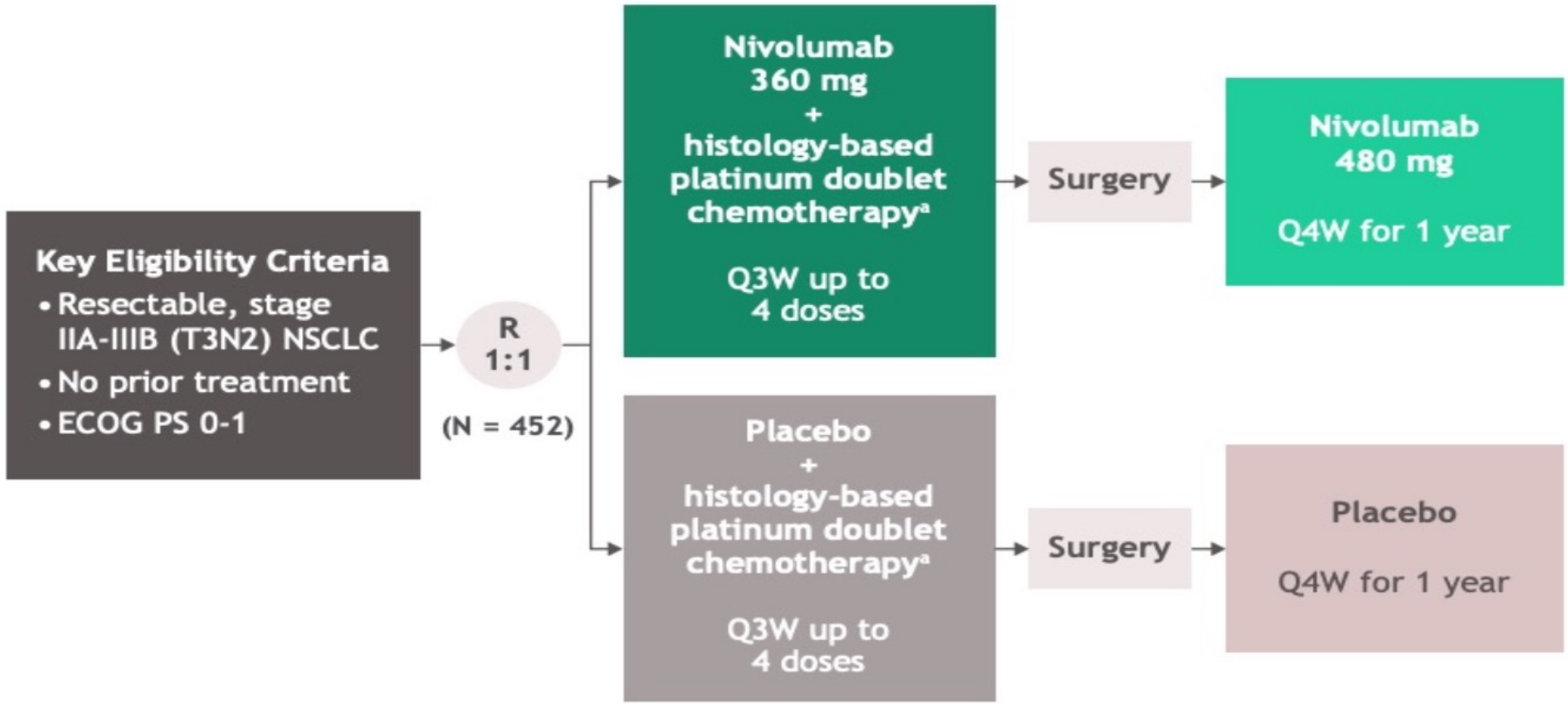
Forde et al. NEJM 2022

CheckMate 816: Safety

Event	Nivolumab plus Chemotherapy (N=176)		Chemotherapy Alone (N=176)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
Adverse events of any cause — no. (%)†				
All	163 (92.6)	72 (40.9)	171 (97.2)	77 (43.8)
Leading to discontinuation of treatment	18 (10.2)	10 (5.7)	20 (11.4)	7 (4.0)
Serious	30 (17.0)	19 (10.8)	24 (13.6)	17 (9.7)
Treatment-related adverse events — no. (%)†				
All	145 (82.4)	59 (33.5)	156 (88.6)	65 (36.9)
Leading to discontinuation of treatment	18 (10.2)	10 (5.7)	17 (9.7)	6 (3.4)
Serious	21 (11.9)	15 (8.5)	18 (10.2)	14 (8.0)
Death‡	0	—	3 (1.7)	—
Surgery-related adverse events — no./total no. (%)§	62/149 (41.6)	17/149 (11.4)	63/135 (46.7)	20/135 (14.8)

Forde et al. NEJM 2022

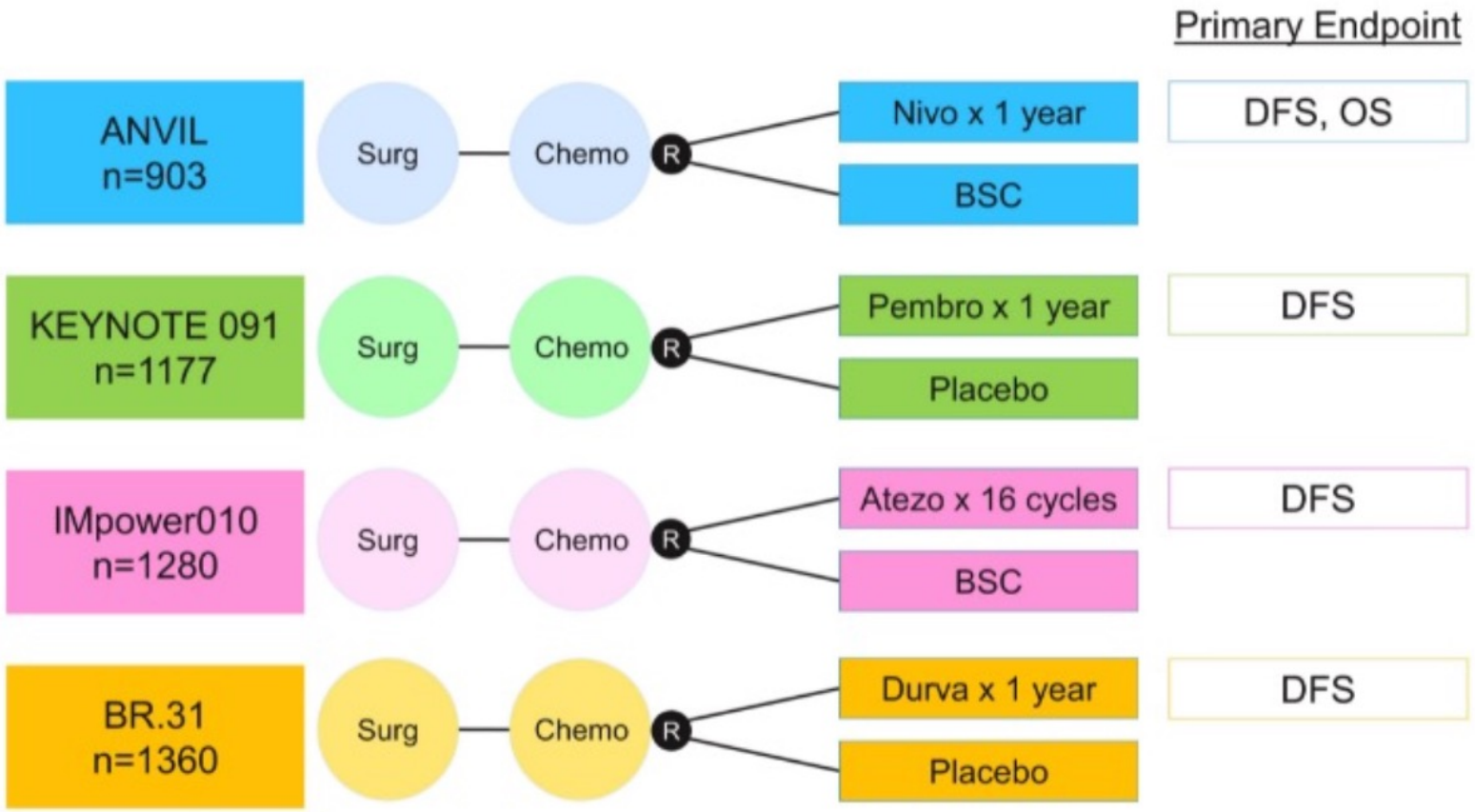
CheckMate 77T



Primary Endpoint: EFS by blinded independent central review

Key Secondary Endpoints: OS; pCR rate by blinded independent pathology review; MPR rate by blinded independent pathology review; AEs; SAEs

Adjuvant studies

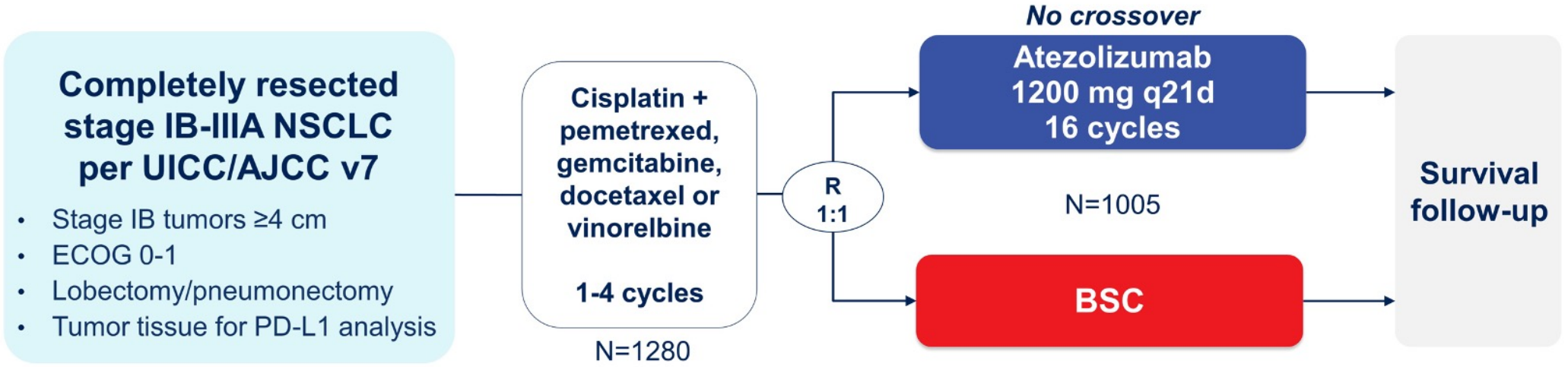


CANOPY–A: Canakinumab vs PBO
Primary Endpoint: DFS

MERMAID-1: Durva + SoC chemo vs SoC chemo
Primary Endpoint: DFS in MRD+ set

MERMAID-2: Durva vs PBO
Primary Endpoint: DFS in PD-L1≥1%

IMpower010: Adjuvant atezolizumab vs BSC

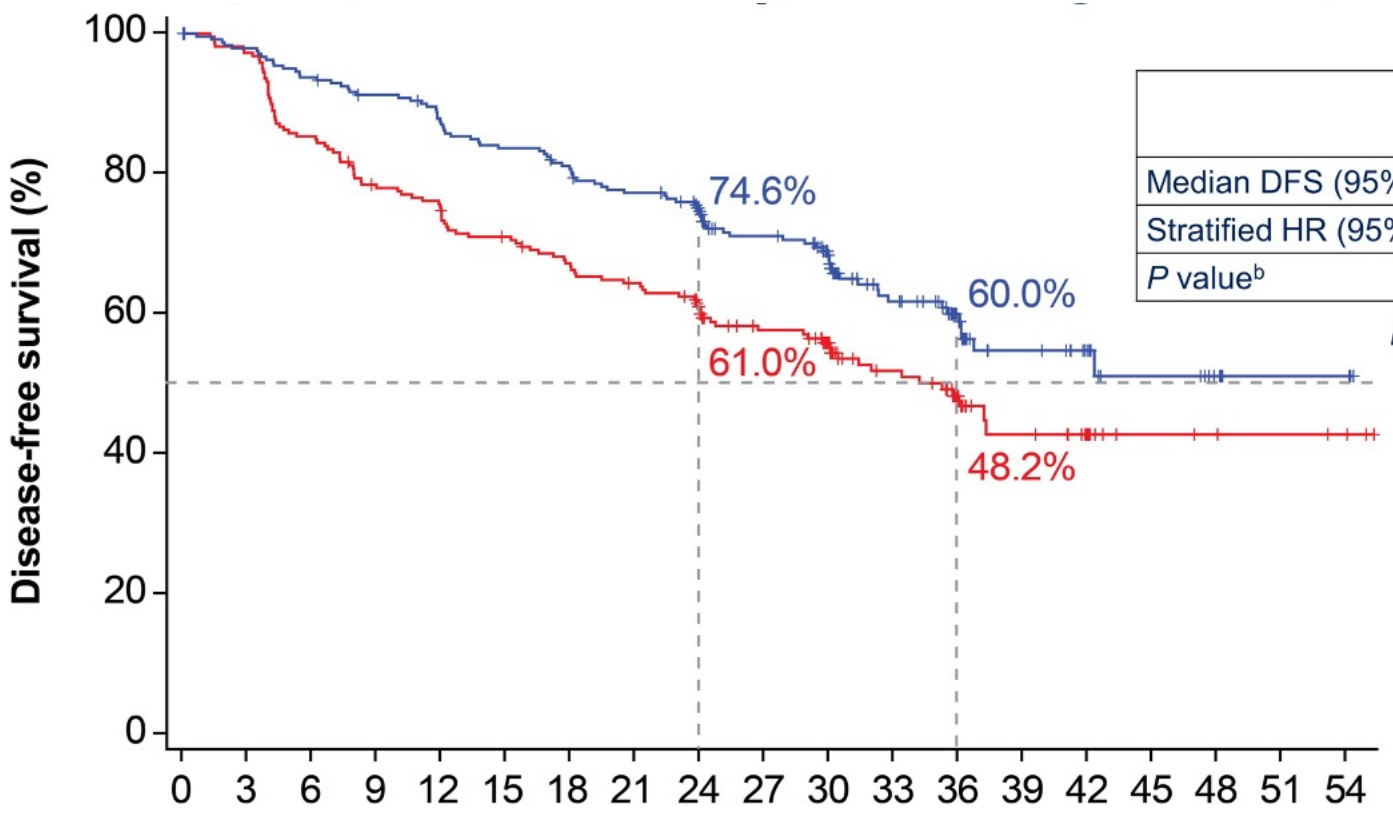


Stratification factors
- Male/female
- Stage (IB vs II vs IIIA)
- Histology
- PD-L1 tumor expression status[a]: TC2/3 and any IC vs TC0/1 and IC2/3 vs TC0/1 and IC0/1

Primary endpoints
- Investigator-assessed DFS tested hierarchically:
  - PD-L1 TC ≥1% (per SP263) stage II-IIIA population
  - All-randomized stage II-IIIA population
  - ITT population (stage IB-IIIA)

Key secondary endpoints
- OS in ITT population
- DFS in PD-L1 TC ≥50% (per SP263) stage II-IIIA population
- 3-y and 5-y DFS in all 3 populations

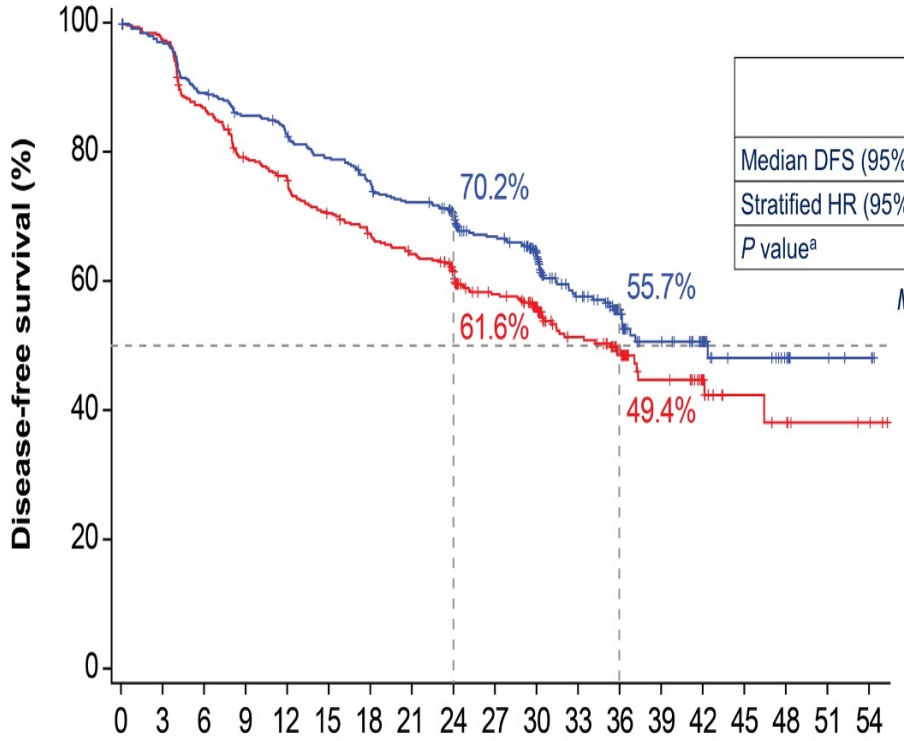
IMpower010: DFS in the PD-L1 ≥ 1% stage II-IIIA population



	Atezolizumab (n=248)	BSC (n=228)
Median DFS (95% CI), mo	NE (36.1, NE)	35.3 (29.0, NE)
Stratified HR (95% CI)	0.66 (0.50, 0.88)	
P value[b]	0.004[c]	

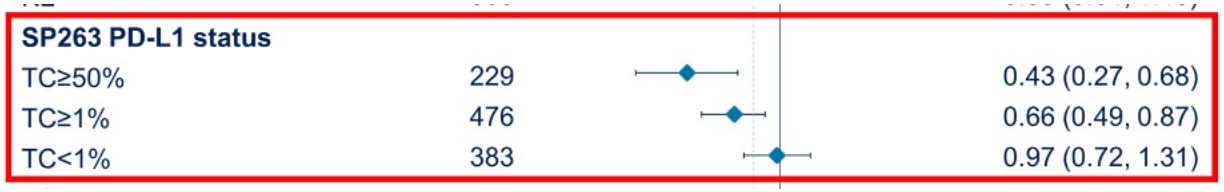
Median follow-up: 32.8 mo (range, 0.1-57.5)

IMpower010: DFS in the all-randomized stage II-IIIA population

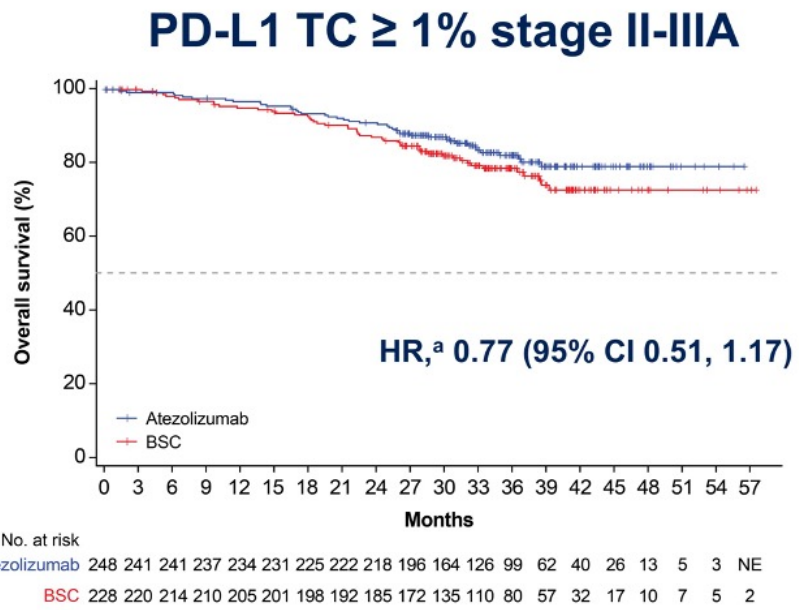


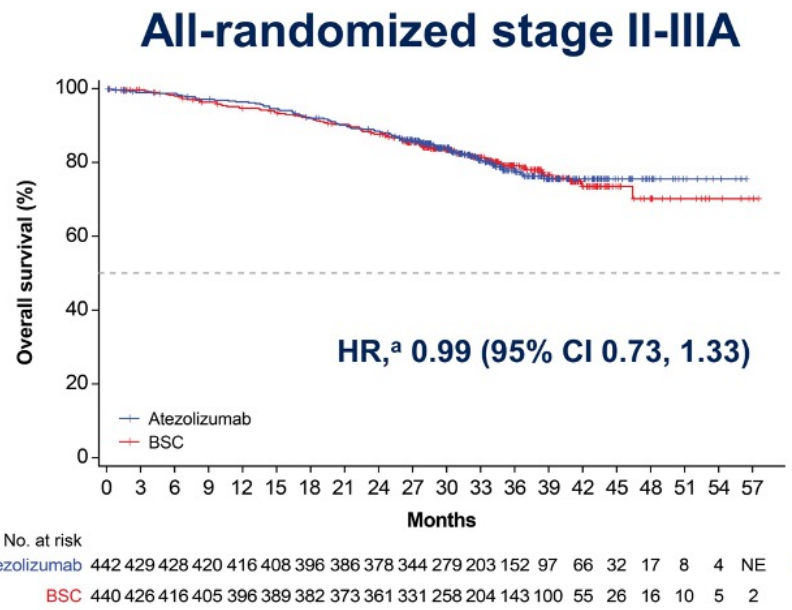
	Atezolizumab (n=442)	BSC (n=440)
Median DFS (95% CI), mo	42.3 (36.0, NE)	35.3 (30.4, 46.4)
Stratified HR (95% CI)	0.79 (0.64, 0.96)	
P value[a]	0.02[b]	

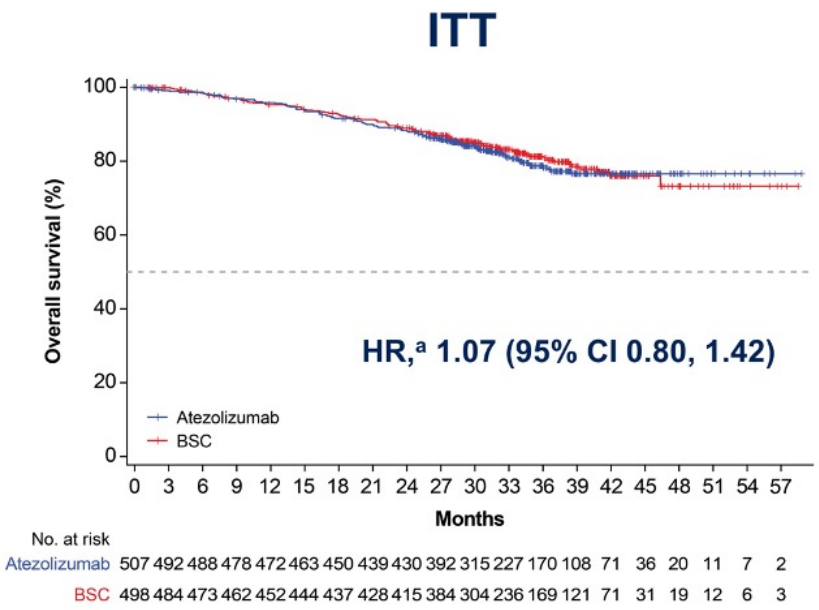
Median follow-up: 32.2 mo (range, 0-57.5)



IMpower010: OS





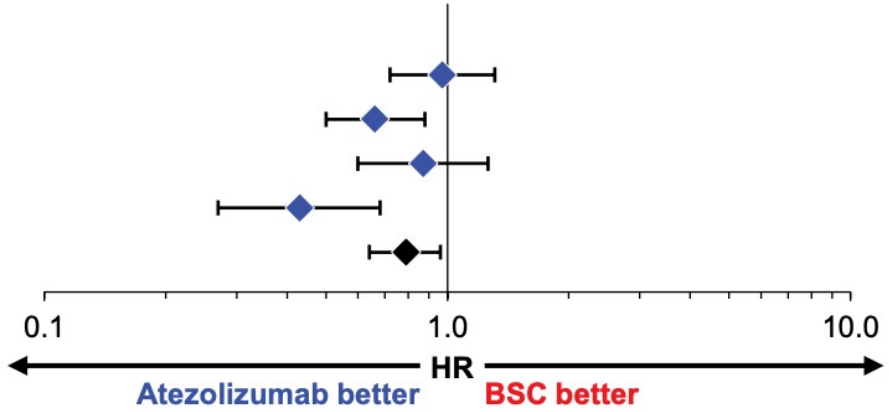


- **OS data were immature at this pre-planned DFS interim analysis**

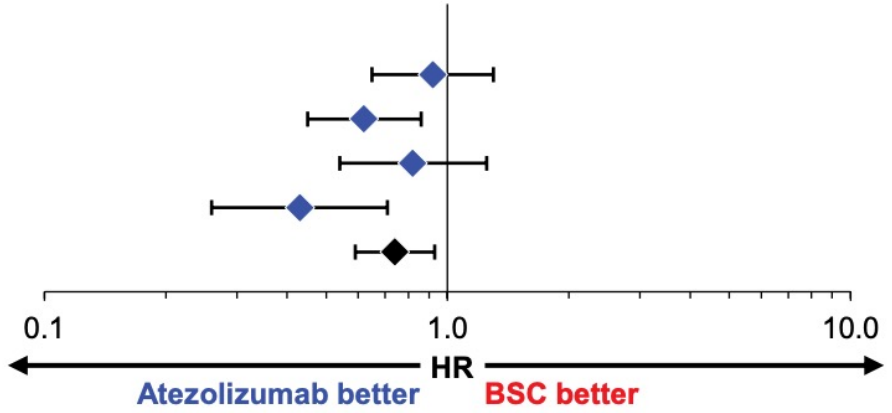
IMpower010: DFS by PD-L1 status

All-randomised stage II-IIIA population (with and without known EGFR/ALK+ disease)

Subgroup *(including EGFR/ALK+)*	n	HR (95% CI)[b,c]
PD-L1 status by SP263		
TC <1%	383	0.97 (0.72, 1.31)
TC ≥1%	476	0.66 (0.50, 0.88)
TC 1-49%	247	0.87 (0.60, 1.26)
TC ≥50%	229	0.43 (0.27, 0.68)
All patients[d]	882	0.79 (0.64, 0.96)

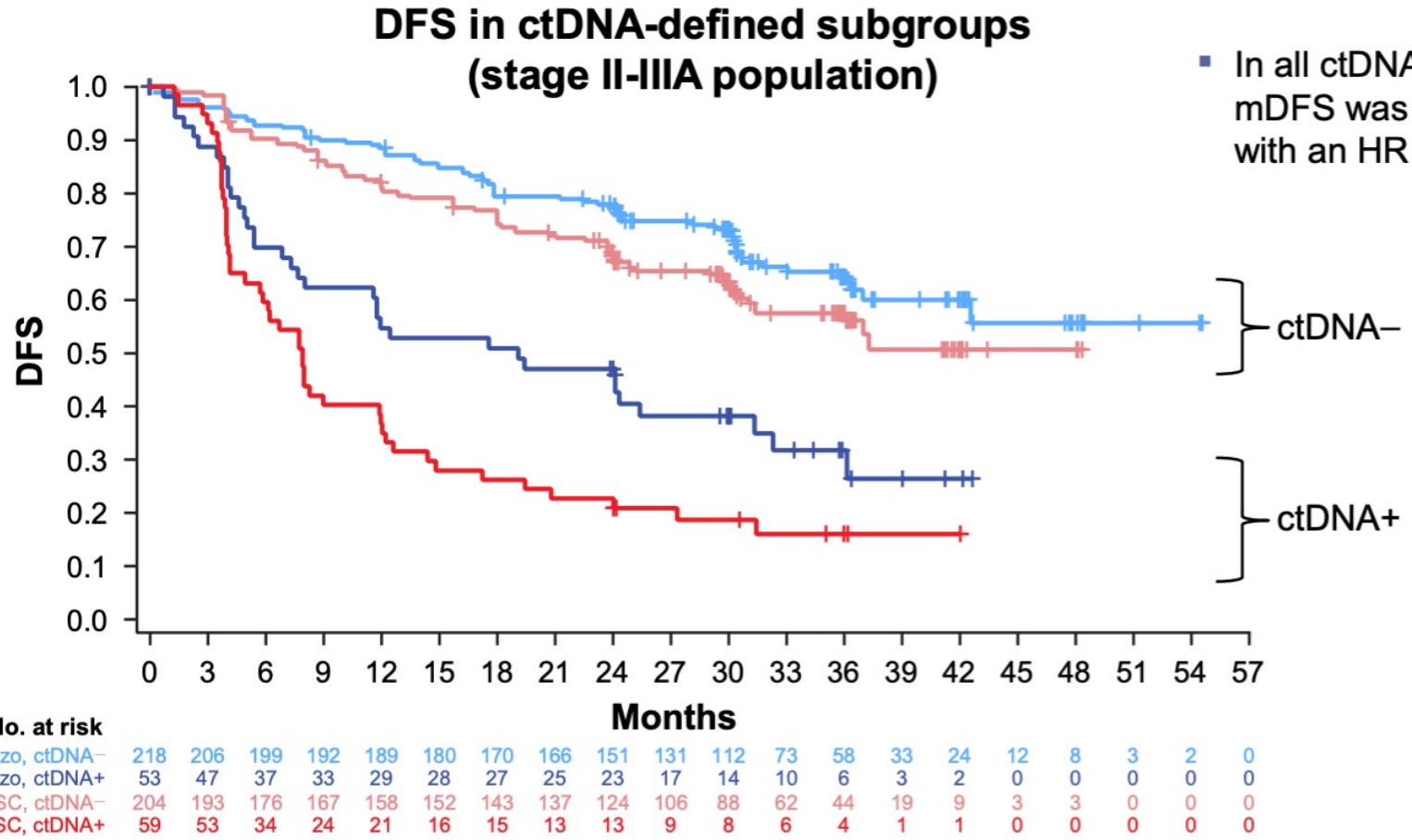


Subgroup *(excluding EGFR/ALK+)*[e]	n	HR (95% CI)[f,g]
PD-L1 status by SP263		
TC <1%	312	0.92 (0.65, 1.30)
TC ≥1%	410	0.62 (0.45, 0.86)
TC 1-49%	201	0.82 (0.54, 1.25)
TC ≥50%	209	0.43 (0.26, 0.71)
All patients[h]	743	0.74 (0.59, 0.93)



Clinical cutoff: 21 January 2021. [a] Per SP263 assay.

IMpower010: DFS favored atezo in both ctDNA+ and ctDNA- patients



- In all ctDNA-evaluable stage II-IIIA patients, mDFS was NR (atezo) vs 31.4 months (BSC), with an HR of 0.69 (95% CI: 0.53, 0.89)

ctDNA–	Atezo (n=218)	BSC (n=204)
mDFS, mo	NR	NR
HR (95% CI)	0.72 (0.52, 1.00)	

ctDNA+	Atezo (n=53)	BSC (n=59)
mDFS, mo	19.1	7.9
HR (95% CI)	0.61 (0.39, 0.94)	

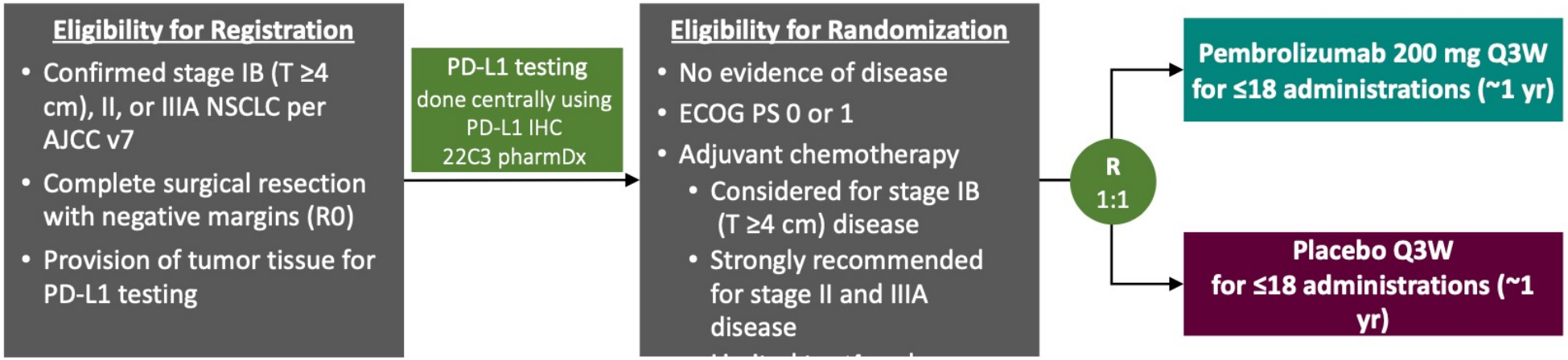
IMpower010: Safety

	Atezolizumab group (n=495)	Best supportive care group (n=495)
Adverse event		
Any grade	459 (93%)	350 (71%)
Grade 3–4	108 (22%)	57 (12%)
Serious	87 (18%)	42 (8%)
Grade 5	8 (2%)*	3 (1%)†
Led to dose interruption of atezolizumab	142 (29%)	..
Led to atezolizumab discontinuation	90 (18%)	..
Immune-mediated adverse events		
Any grade	256 (52%)	47 (9%)
Grade 3–4	39 (8%)	3 (1%)
Required the use of systemic corticosteroids‡	60 (12%)	4 (1%)
Led to discontinuation	52 (11%)	0

Felipe et al. Lancet 2021

PEARLS/KEYNOTE 091

Randomized, Triple-Blind, Phase 3



Stratification Factors

- Disease stage (IB vs II vs IIIA)
- PD-L1 TPS (<1% vs 1-49% vs ≥50%)
- Receipt of adjuvant chemotherapy (yes vs no)
- Geographic region (Asia vs Eastern Europe vs Western Europe vs rest of world)

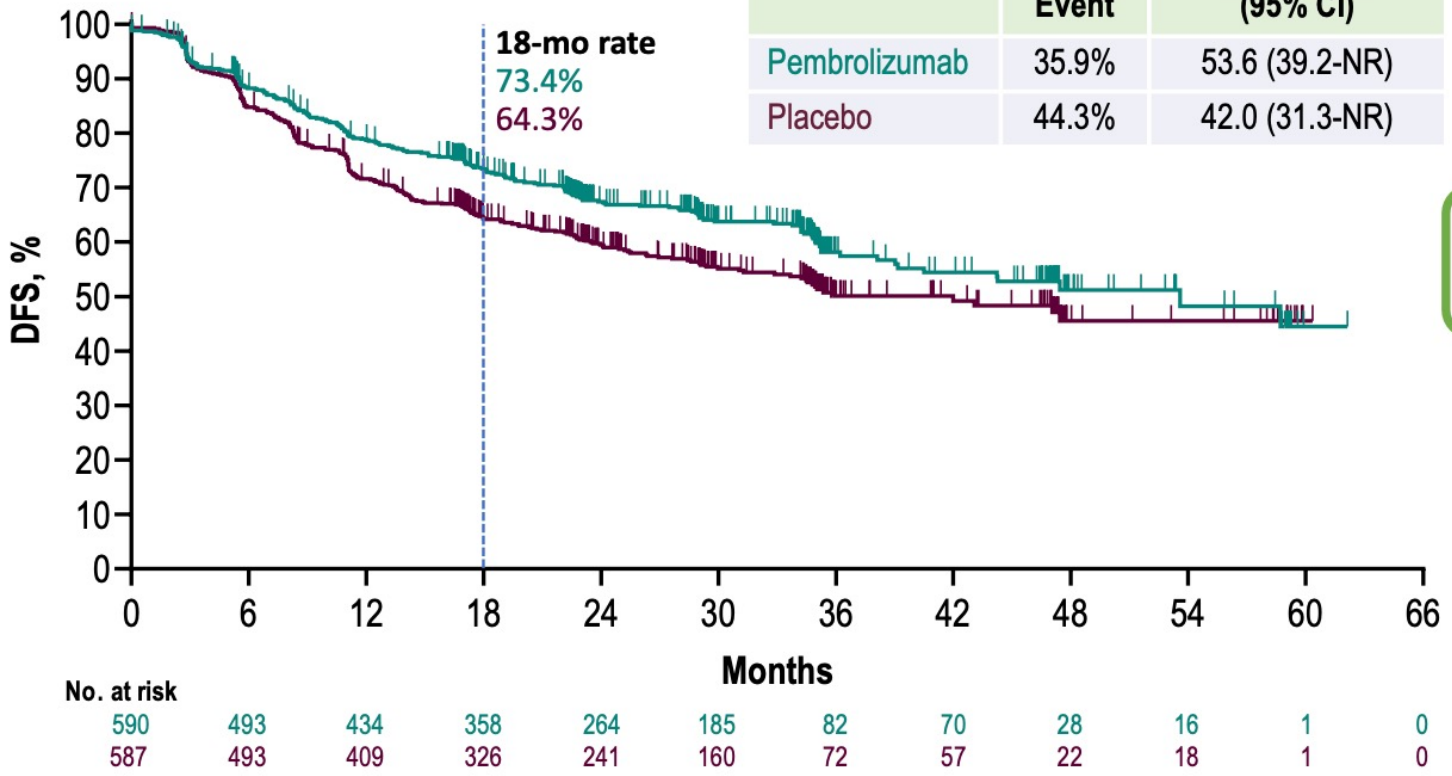
Dual Primary End Points

- DFS in the overall population
- DFS in the PD-L1 TPS ≥50% population

Secondary End Points

- DFS in the PD-L1 TPS ≥1% population
- OS in the overall, PD-L1 TPS ≥50%, and PD-L1 TPS ≥1% populations
- Lung cancer-specific survival in the overall population
- Safety

PEARLS/KEYNOTE 091: DFS Overall Population

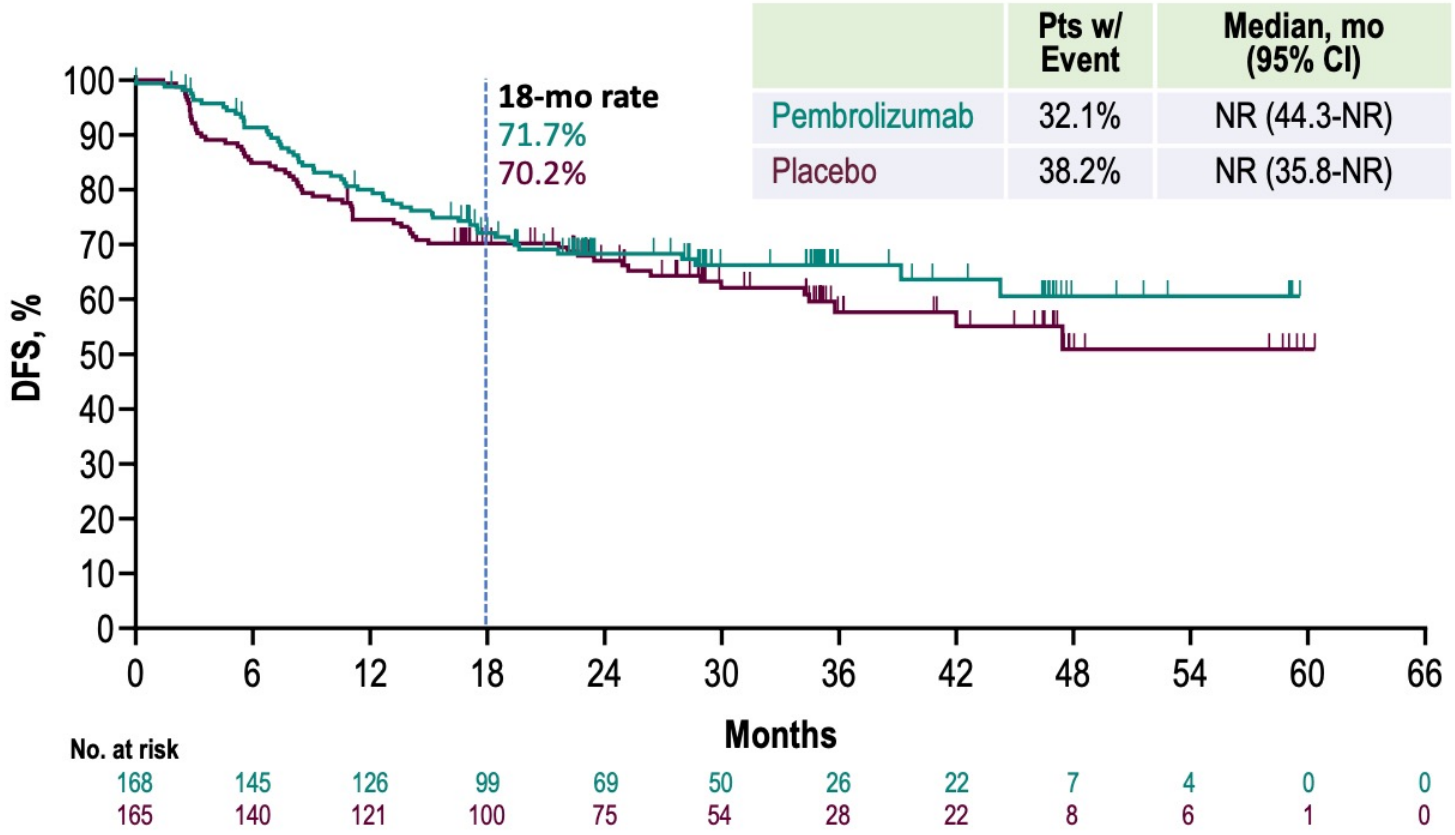


	Pts w/ Event	Median, mo (95% CI)
Pembrolizumab	35.9%	53.6 (39.2-NR)
Placebo	44.3%	42.0 (31.3-NR)

HR 0.76 (95% CI, 0.63-0.91)
***P* = 0.0014**

Response assessed per RECIST v1.1 by investigator review.
Data cutoff date: September 20, 2021

PEARLS/KEYNOTE 091: DFS PD-L1 TPS ≥50%

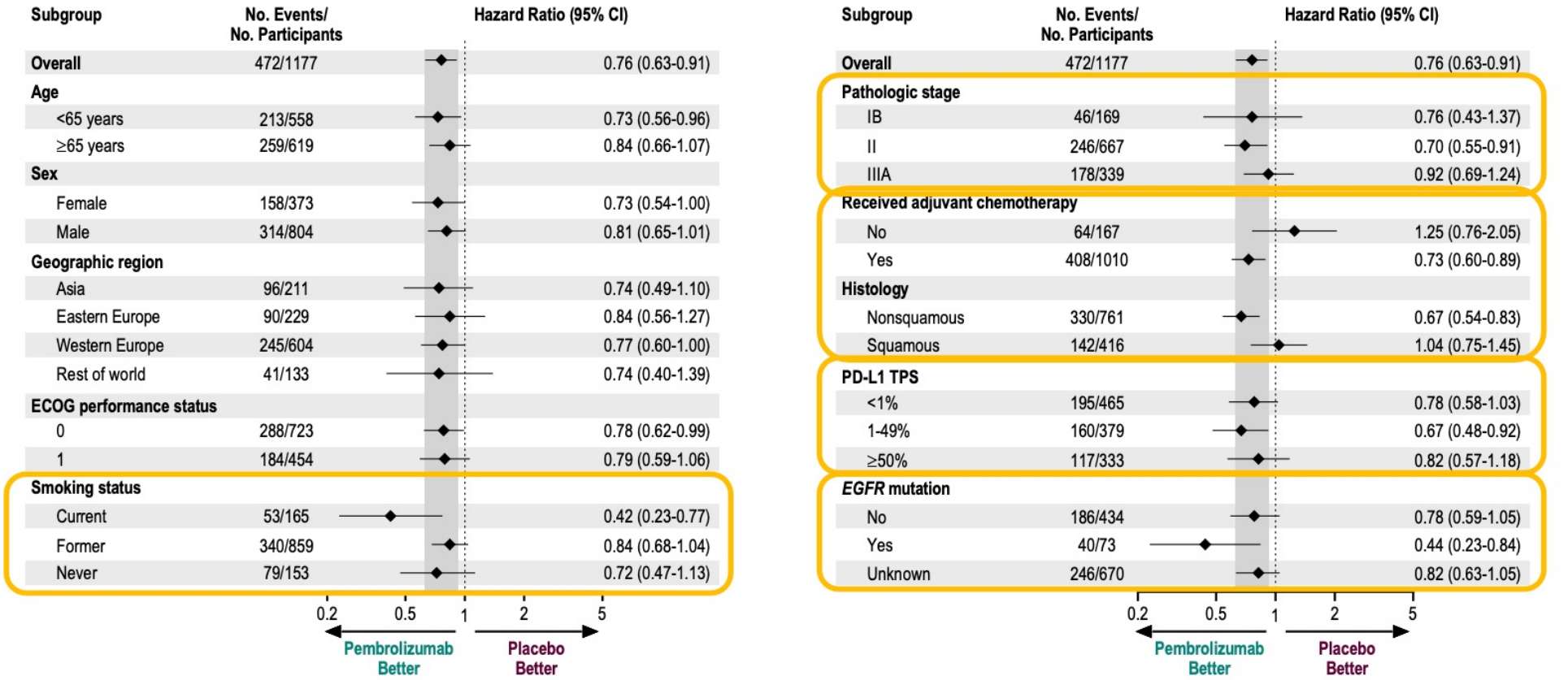


	Pts w/ Event	Median, mo (95% CI)
Pembrolizumab	32.1%	NR (44.3-NR)
Placebo	38.2%	NR (35.8-NR)

HR 0.82 (95% CI, 0.57-1.18)
***P* = 0.14**

Response assessed per RECIST v1.1 by investigator review.
Data cutoff date: September 20, 2021

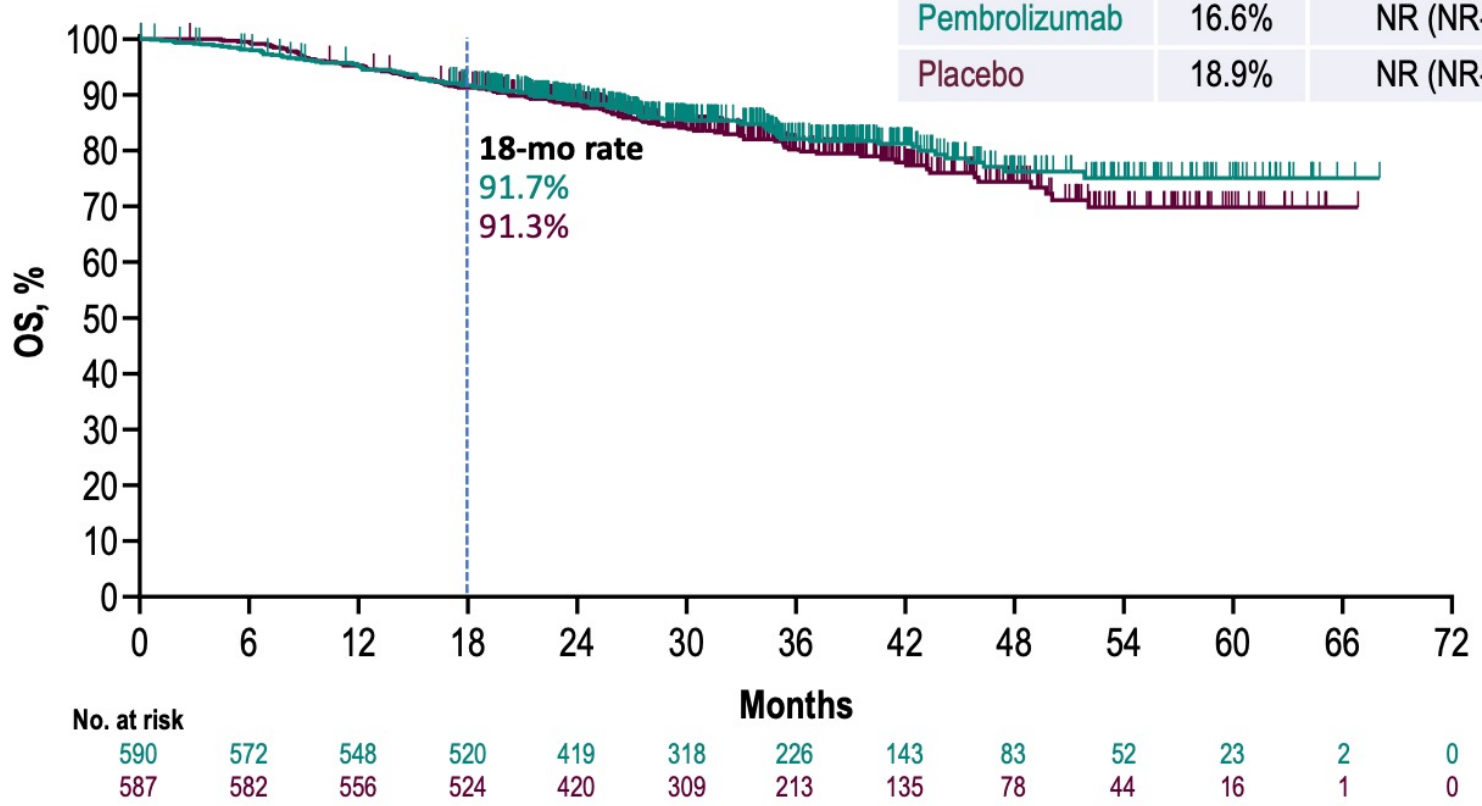
PEARLS/KEYNOTE 091: DFS Key Subgroups



Response assessed per RECIST v1.1 by investigator review.
Data cutoff date: September 20, 2021

PEARLS/KEYNOTE 091: OS

	Pts w/ Event	Median, mo (95% CI)
Pembrolizumab	16.6%	NR (NR-NR)
Placebo	18.9%	NR (NR-NR)



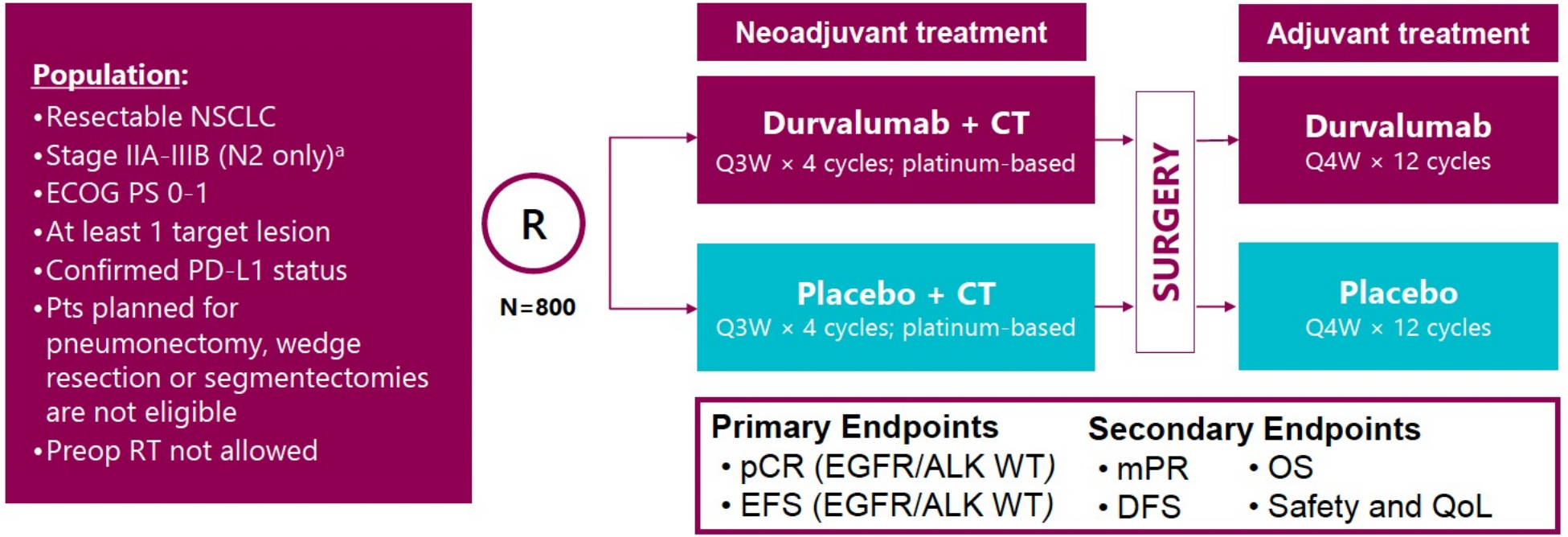
HR 0.87 (95% CI, 0.67-1.15)
***P* = 0.17**

Secondary Endpoint, IMMATURE
Data cutoff date: September 20, 2021

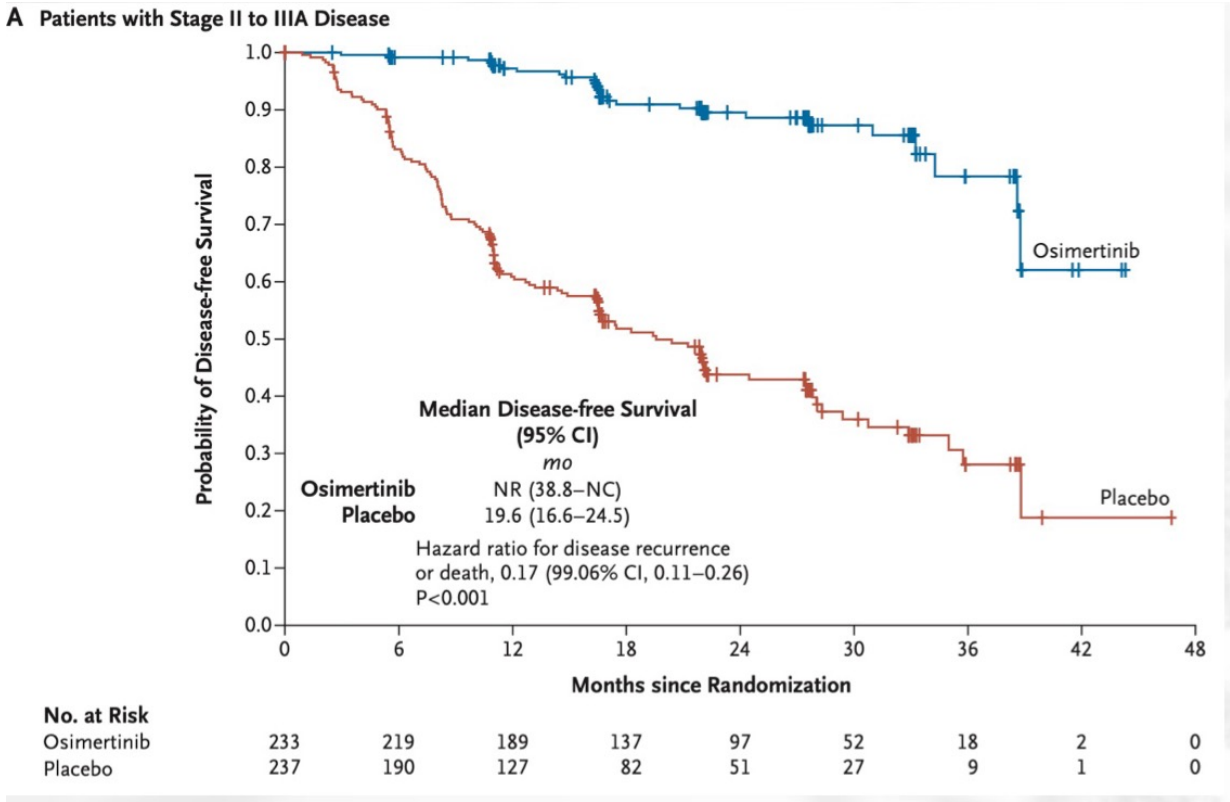
AEGEAN: Study Design

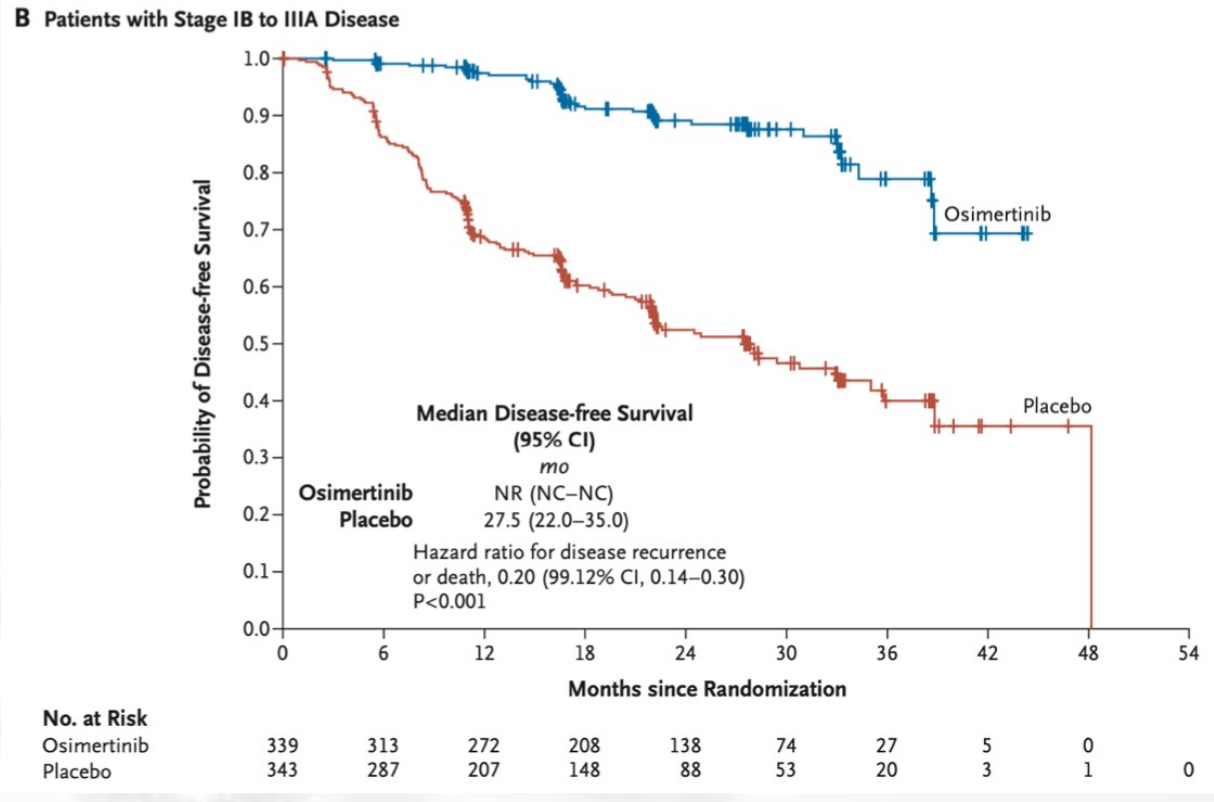
A Phase 3 trial of neoadjuvant/adjuvant durvalumab vs placebo in resectable Stage II-III NSCLC

Press Release published June 30, 2022
AEGEAN: Improved pCR in Resectable Stage II-III NSCLC

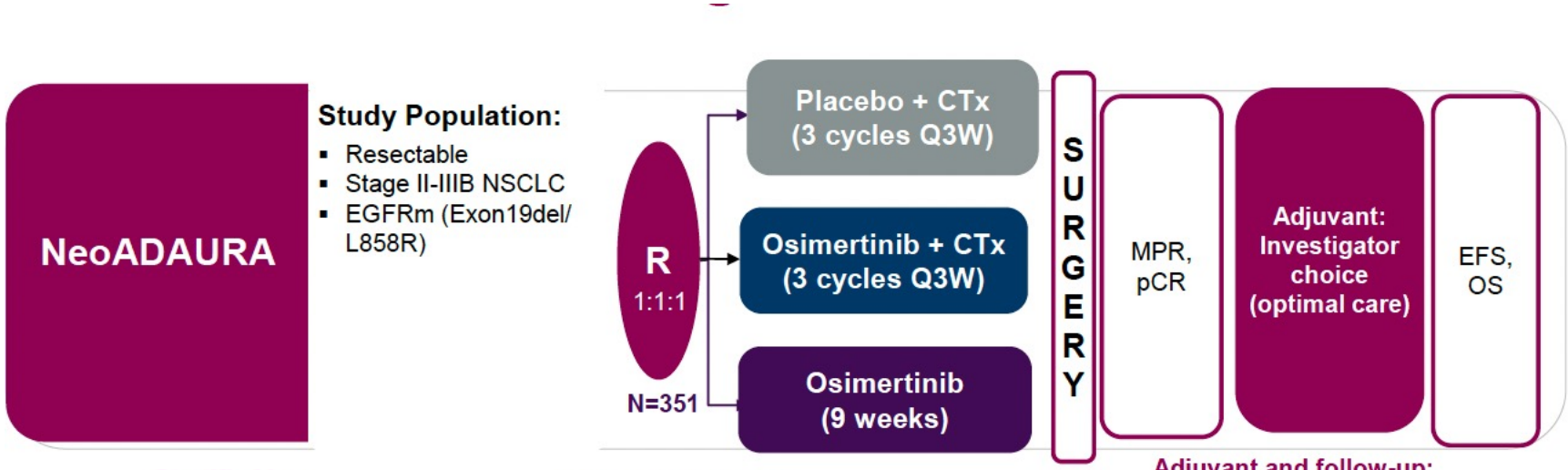


ADAURA: DFS benefit with adjuvant osimertinib





NeoADAURA: Trial Design



Stratified by:

- Stage II/ Stage III
- Non-Asian/ Chinese/other Asian
- EGFRm (Exon19del/L858R)

Double blind arms:

- Placebo QD plus investigators' choice of platinum-based CTx (three 21-day cycles of carboplatin AUC_5 plus pemetrexed 500 mg/m^2 or cisplatin 75 mg/m^2 plus pemetrexed 500 mg/m^2)
- Osimertinib 80 mg QD plus investigators' choice of CTx (as above)

Open-label:

- Osimertinib 80 mg QD monotherapy for ≥9 weeks

Adjuvant and follow-up:

- OS: 5 years from surgery, with evaluations at 12 and 24 weeks post surgery then every 24 weeks
- Osimertinib offered to all patients that completed surgery (± postsurgical CTx for up to 3 years or disease recurrence)

Primary Endpoints

- MPR

Secondary Endpoints

- pCR
- Downstaging: N2 to N1/N0 and N1 to N0 at the time of surgery
- DFS
- OS
- MPR in patients with/without detectable EGFRm in plasma
- ctDNA at screening
- Disease-related symptoms and HRQoL
- Safety and tolerability

NCT04351555

Take home messages

- IMpower010 led to FDA approval of adjuvant atezolizumab in patients with NSCLC with PD-L1 ≥ 1% and has led to change in clinical practice.
- PD-L1 testing and NGS testing should be performed for patients with resected NSCLC.
- If EGFR mutation+ → platinum chemotherapy → osimertinib
- If EGFR mutation - / PD-L1 positive → platinum chemotherapy → atezolizumab
- Individualized decisions should be made if other driver mutation is identified and/or PD-L1 1-49%.

Take home messages

- CheckMate 816 has led to approval of neoadjuvant chemoimmunotherapy for resectable NSCLC.
- Data suggests pembrolizumab has the potential to be a new adjuvant treatment option for patients with stage IB to IIIA NSCLC following complete resection and adjuvant chemotherapy, regardless of PD-L1 expression.
- Ongoing phase 3 trials of adjuvant and neoadjuvant immunotherapy regimens will provide further insights into new treatment algorithms for resectable NSCLC


1365
WINSHIP
CANCER
INSTITUTE
OF
EMORY UNIVERSITY
NCI
Comprehensive
Cancer Center
A Cancer Center Designated by the
National Cancer Institute

Thank you!